REMARKS

Review and reconsideration of the Office Action dated January 10, 2005, is respectfully requested in view of the above amendments and the following remarks.

Claims 1, 10, 11, and 32 to 36 are under consideration. Claims 1, 10, and 11 have been canceled. Claims 14 and 17 to 31 were previously withdrawn from further consideration pursuant to 37 CFR 1.142(b).

Support for Claim 32 can be found at paragraphs [00120] - [00140]; support for Claim 33 can be found at paragraphs [00117]-[00131]; support for Claim 34 can be found at paragraph [00117]; support for Claim 35 can be found at paragraph [00127]; and support for Claim 36 can be found at paragraph [00131]. Applicant has been careful and not added new matter to the Specification.

Office Action

Turning now to the Office Action in greater detail, the paragraphing of the Examiner is adopted.

Claim Rejections under 35 USC 112, First paragraph

The Examiner has rejected Claims 1 to 13, 15, and 16 for containing subject matter that the Examiner believes to be inadequately described in the specification. Below, the Applicant addresses the comments put forth by the Examiner on pages 5 to 7 of the Action.

The Applicant believes that the specification indeed provides adequate description of a process for preparing an immunogenic peptide mixture. A number of such mixtures are described in the Examples. Specifically, mixtures directed to

various pathogens (HIV, hepatitis and influenza) are disclosed, and the preparation of such mixtures is based directly on the method provided. The Applicant believes that the process described and claimed has wide applicability to a number of pathogens, and does not wish to limit the invention to a particular pathogen.

Further, to limit the process for preparing a mixture to the extent that it would recite particular peptides from an exemplary mixture would be overly limiting to the invention. Given that *process* claims have been elected, the Applicant does not now wish to be limited to a particular formulation by being forced to recite sequences.

The Applicant believes that a structural formula is not necessary to enable the making of a peptide mixture. There are exemplary descriptions of the structures of a variety of immunogenic epitopes of a number of pathogens. Further, in the examples provided, it would be clear that identification of common or variable residues would be based on the immunogenic epitope sequences obtained in the step of "obtaining".

The Applicant advises that those skilled in the art would understand how (and where) to obtain information regarding immunogenic epitope sequences for any variety of pathogens. Exemplary sequences are taught for HIV, influenza, and HCV in the application. These pathogens are each the subject of databases maintained and overseen by the National Institutes of Health. For the Examiner's convenience, specific urls for the databases directed to these pathogens are:

HIV: http://hiv-web.lanl.gov/content/index

Influenza: http://www.flu.lanl.gov/

HCV: http://hcv.lanl.gov/content/hcv-db/index

As the Examiner must be well aware of, sequence data is best represented, maintained and searched electronically, and the skilled artisan in the area of biological sequences would know that web-based databases, or other types of electronic data repositories are the only practical way in which sequence data can be curated. Each of these databases was available as of the filing date of the instant application, and this can be verified by the Examiner by contacting the National Institutes of Health at 301-496-4000.

The following representative link demonstrates that the HIV sequence database has been available and accessible since 1995:

http://hiv-web.lanl.gov/content/hiv-b/HTML/compendium.html.

The following link provides a map for immunogenic CTL, T helper, and antibody epitopes in any/all HIV proteins of interest:

http://hiv-web.lanl.gov/content/immunology/maps/maps.html.

HIV is an exemplary model of the type of databases and information commonly known and used by those in the field. It is illogical, therefore, NOT to extend this to other pathogens for having immunogenic epitope sequences.

Although it is true that numerous pathogens may be or could be used in the method of the invention, the Applicants do not believe that specific sequences need to be recited, provided a person skilled in the art would know where to find or how to derive such sequences.

The Examiner states that synthesis of a peptide requires a structure to enable synthesis, such as for chain lengthening. This is precisely the process that the instant claim set is directed to. The process outlines the steps needed to *arrive at*

the amino acids that are to be added in a chain lengthening procedure.

The Examiner notes that pathogens undergo variability and mutations. It is on the basis of this observation that the instant invention was arrived at. The regions that are common (or conserved) in a pathogen will not show mutations, and for purposes of the claimed process, would be considered "common". However, the variable regions are ones that have variability. This will be evident from the sequences found in the step of "obtaining". It is true that a pathogen can comprise numerous epitopes, but defining a structure would limit the invention to one specific epitope for one specific pathogen. A person skilled in the art can identify an epitope that has variability, and the Applicants assert that any such epitope could be relied upon to formulate a mixture according to the claimed process. The immunogenicity of such a mixture could then be tested as outlined in the examples of the application.

In the step of obtaining, the term "immunogenic epitope sequences" may have caused some confusion for the Examiner. The term is defined by the claim language (see Claim 1), specifically: "said immunogenic epitope sequences having a common residue region and *at least one variable residue*...". The Applicants believe this is an adequate definition to allow a person skilled in the art to locate an immunogenic epitope sequence from a pathogen. Areas of antigenic variation are ***by definition*** immunogenic epitopes. It is known in the art, and there is adequate data to support that immunity drives antigenic variation. Thus, wherever variability is observed, this is because an immunogenic region of the sequence was varied or mutated, thereby avoiding detection. Thus, it is believed that

the claim language is adequately descriptive to allow identification of immunogenic epitopes.

The Examiner recites a quote from University of California v. Eli Lilly (1997), but this quote is not relevant to process claims *per se* since chemical structures. The formulae or chemical names required in that case were relevant to composition of matter claims. The instant claims are process claims. For processes that may be applied in more than one circumstance or with a variety of different materials, the Applicant is not aware of a requirement to recite a particular chemical structure on which the process must be enacted.

The Applicant agrees that the process now described and claimed could indeed be relevant to a large number of different pathogens. Exemplary pathogens are discussed (HIV, HCV and Influenza) in adequate detail for a person skilled in the art to apply the process to these or other pathogens. Thus, to restrict the invention to the exemplary embodiments would appear to be unduly limiting when mere substitution of one pathogen for another is all that is required for a person to practice the invention with a non-exemplified pathogen.

It is believed that with amendments now in place in Claim 1 that the invention is fully supported. The "threshold frequency" for each pathogen has now been set at 12%. For example, if an amino acid is found at a particular residue with a frequency of 10%, it would not meet the threshold, and would not be a candidate for the variable residue position. If another amino acid is found with a frequency of 40%, it would exceed the threshold of 12%, and in the step of rounding, this particular amino acid would round to 50% (the nearest 25% meaning either 25%, 50%, 75%). The threshold of 12% is relevant to all

pathogens subject to this process. It is hoped that this explanation clarifies the threshold frequency for the Examiner, in context of the comments made on page 7 of the Action.

Withdrawal of the rejection is respectfully requested.

Claim Rejections under 35 USC 102

The Examiner objected to Claims 1 to 13 and 15-16 as being unpatentable due to anticipation in view of the reference of Anderson *et al*. The Applicant has amended Claim 1 to include the limitations previously found in Claims 2 to 9. All other claims under consideration now depend from amended Claim 1.

Applicant traverses this rejection.

The teachings of Anderson *et al*. do not anticipate Claim 1 as amended. For example, there is no implication in Anderson *et al*. that the number of different peptides in the mixture be limited. The desire to limit the complexity was not discussed in this or any other prior art document. Moreover, the process described by Anderson *et al*. would not give rise to a vaccine that is commercially viable, because the complexity of the mixture would be too onerous to characterize, for example in order to meet regulatory approval requirements. The mixture prepared according to Anderson *et al*. would lead to over 32,000 variants see table 1 on page 737). Characterization of the mixture alone would be an onerous task. On page 736 (final sentence) Anderson *et al*. state: "Thus, in a single synthesis, a HEC consisting of a mixture of peptides representing ***all*** the observed *in vivo* variants of an epitope was produced." [emphasis added]. This passage indicates that there was no recognition that limiting the complexity of the mixture was desirable or posed any advantage to the mixture whatsoever. By contrast,

Claim 1, as now amended, clearly limits the number of peptides in a mixture to between 2 and 64. This limitation was previously found in now canceled Claim 13. This means that a peptide mixture can have at maximum 6 variable residues, when only 2 options per variable residue are identified, leading to a total number of peptides of 2^6 or 64. The process now claimed in Claim 1 has a number of other distinctions not taught by Anderson *et al.* In particular, the rules by which amino acids representing variable residues are selected are clearly presented, in terms of a threshold frequency which must be identified, a rounding step that is not employed in the Anderson *et al.* paper. Add to these differences the limits now imposed on the number of peptides in the mixture, as now specified in Claim 1, and it is believed that Claim 1 as now amended is not anticipated by Anderson *et al.*

In the discussion section of the Anderson *et al.* paper (page 739, second paragraph), it is stated that an "HEC, representing ***tens of thousands*** of slightly different variations of an epitope, should ensure that peptides will exist which can overcome the problems described above" [emphasis added]. This passage clearly illustrates that Anderson *et al.* did not intend to limit the number of peptides in the mixture, and teaches away from the effectiveness of a mixture with a limited number of peptides. This statement alone should serve to illustrate to the Examiner that Anderson *et al.* did not anticipate any use of a mixture containing limited numbers of peptides, and provided no methodology by which such a mixture could be formulated.

Withdrawal of the rejection is respectfully requested.

Claim Rejections under 35 USC 103

Claims 1 to 10 and 15-16 were rejected on the ground of being obvious and thus unpatentable under 35 USC 103 in view of the teachings of Anderson *et al.*, but not in combination with any other prior art document. The rationale put forth in support of the novelty of new Claim 1 over the Anderson *et al.* reference is now applied to support the inventiveness of new Claim 1, but is not reiterated here in the interests of brevity.

Applicant traverses this rejection.

The cited reference does not teach all of the claimed subject matter now present in Claim 1. The missing subject matter is not provided in any other reference provided by the Examiner. The Applicant herein provides rationale as to why the Examiner has failed to meet the burden of factual support for *prima facie* obviousness, and why an obviousness objection on this basis could not be applied to Claim 1 as amended.

No case has been established for *prima facie* obviousness. According to MPEP 2143, the three basic criteria for establishing *prima facie* obviousness are 1) suggestion or motivation in the references themselves or generally that the references be modified to combine the teachings; 2) reasonable expectation of success; 3) a teaching or suggestion that the combination be made, and the expectation of success must both be found in the prior art (not in the Applicant's disclosure). These criteria are referred to herein as the first criterion, the second criterion, and the third criterion.

The first criterion for establishing *prima facie* obviousness has not been met. Anderson *et al.* do not provide suggestion or motivation (either within the reference itself or generally) that the teachings relating to a process for forming

a highly complex mixture having over 32,000 peptides could be modified or extended to arrive at the method now described. There is no motivation provided to reduce the number of peptides in the mixture, as now recited in Claim 1 (from 2 to 64 peptides). Additionally, there is no motivation to employ a rounding step to the nearest 25%. In fact, in Table 1 of Anderson *et al.*, none of the peptides for which two variations of an amino acid are used has been rounded to the nearest 25%. The percentages noted are either 80%:20% or 70%:30%. Not one of the variable residues noted n Table 1 of Anderson *et al.* have an amino acid present at 25%, 50% or 75%, as now specifically indicated in claim 1 as amended. There is no motivation provided in Anderson *et al.* to modify the process to reflect the process as now found in Claim 1 with the simplified mixture, or with the rounding step that would only allow certain percentage ratios of differing amino acids at the variable residues. Anderson *et al.* had no motivation to reduce the options, and thus would present the amino acids at a variable residue in any proportion that appeared to be similar to the variability found in the assessed sequences. Although 80:20 and 70:30 are typical in this paper, there is no suggestion of an inclination to systemize this decision-making process when deciding on a ratio. Thus, according to Anderson *et al.*, a variety of ratios would be permitted. According to the instant process claimed in amended Claim 1, an amino acid represented in a variable residue at a ratio other than 25%, 50% or 75% would not be permitted.

The second criterion for establishing *prima facie* obviousness has not been met. Specifically, there was no reasonable expectation of success for formulations having between 2 and 64 peptides in the mixture. The discussion section

specifically emphasizes that "tens of thousands" of slightly different variations of an epitope is the feature that "ensures" that peptides can overcome the problems described. To read into this that a peptide mixture having 64 variations would be adequate is counter-intuitive. Anderson *et al.* specifically teach away from success of a mixture having such a limited number of peptides. Yet it is this very feature that the Applicant now recites in Claim 1, and the specification itself illustrates the efficacy of a formulation prepared by this process.

The third criterion for establishing *prima facie* obviousness has not been met, in particular, there is no teaching or suggestion that a combination (or modification) be made to the teachings of Anderson *et al.* Nowhere is it suggested or taught in any reference or combination of references that a reduced number of peptides would be desirable or functional, or that a rounding step should be included as a way of rationalizing the reduced number of variations for a given residue. There is no acknowledgement in Anderson *et al.* that a mixture having tens of thousands of different peptides would not be commercially viable. The mixture taught by Anderson *et al.* would function to satisfy academic interests at best, but does not provide a practical solution to the problem of formulating an immunogenic peptide mixture.

The Examiner has not produced any other reference that can be combined with Anderson *et al.* to provide the missing features and limitations that are now recited in Claim 1 as amended. Thus, it is requested that the obviousness objection raised to the claims be revisited and withdrawn.

All dependent claims not specifically discussed herein are now ultimately dependent upon independent Claim 1. Any reference applied against the dependent claims would not make up for the deficiencies of the reference to supply the requisite information, as discussed above, to arrive at the invention. The prior art reference applied does not disclose the characterizing features of independent Claim 1, as discussed above, or any dependent claim. Hence, it is respectfully submitted that all of the pending claims as amended herein are patentable over the prior art.

Withdrawal of the rejection is respectfully requested.

Favorable consideration and early issuance of the Notice of Allowance are respectfully requested. Should further issues remain prior to allowance, the Examiner is respectfully requested to contact the undersigned at the indicated telephone number.

Respectfully submitted,

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Date: **May 10, 2005**

CERTIFICATE OF MAILING AND AUTHORIZATION TO CHARGE

I hereby certify that a copy of the foregoing AMENDMENT A for U.S. Application No. 10/072,084 filed February 8, 2002, was deposited in first class U.S. mail, postage prepaid, addressed: Mail Stop: Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria VA 22313-1450, on **May 10, 2005**.

The Commissioner is hereby authorized to charge any additional fees, which may be required at any time during the prosecution of this application without specific authorization, or credit any overpayment, to Deposit Account No. 16-0877.

Yaté K. Cutliff